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DOI: https://doi.org/10.1097/AIA.0000000000000119

# Do Amide Local Anesthetics Play a Therapeutic Role in the Perioperative Management of Cancer Patients?

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Cancer is one of the leading causes of morbidity and mortality worldwide, with about 14 million estimated new cases and 8 million deaths annually.[1] For solid tumors such as breast cancer, surgical removal remains an essential and vital part of the overall treatment strategy.[2] However, the perioperative period is increasingly recognized as a timepoint with the potential to influence patient outcomes profoundly.[3] First, the mechanical process of tumor resection and subsequent regenerative processes may promote the recurrence of local residual disease. Second, perioperative immunosuppression may impair the host's ability to attack circulating tumor cells (CTCs) or distant micrometastases. Third, some drugs administered perioperatively, such as opioids, have been alleged to promote tumor growth in their own right.[3]

Therefore, theoretically, regional anesthetic strategies, using local anesthetics to reversibly block nerve impulse propagation, seem to be ideally suited to treat perioperative cancer patients. These techniques, among their other effects, decrease the surgical stress response, preserve

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INTERNATIONAL ANESTHESIOLOGY CLINICS
*Volume 54, Number 4, e17–e32, DOI: 10.1097/AIA.0000000000000119*

the patient's immune system to a greater extent than general anesthesia, and reduce the need for opioids.[4,5] In addition to these indirect effects, direct cytotoxic effects of local anesthetics on tumor cells as well as modulation and inhibition of subcellular pathways essential to tumor progression and metastasis have been described experimentally.[6] This review will thus aim to outline experimental and clinical evidence of how local anesthetics might be able to interfere with processes important for the pathogenesis of metastasis during the perioperative period and to summarize preclinical and clinical evidence supporting their use leading to a possible better patient outcome.

## ■ The Clinical Challenge: CTCs → Metastasis

CTCs are released from the primary tumor into the circulation or the lymphatic system and might then be able to form new metastases.[7] The number of CTCs can be correlated with the patient outcome and has been established as an independent prognostic factor for survival in metastatic breast, colon, and prostate cancer.[8] The concept of CTCs and their contribution to metastasis and therefore a possible worsened outcome was first described in 1963 and has gained more and more attention over the last couple of years.[9] Depending on the type of tumor, the stage of the disease and possible prior treatments (eg, neoadjuvant chemotherapy), the number of CTCs that can be detected at a given timepoint during the course of the disease might differ substantially.[10–12] However, it has also been demonstrated that there might be a significant increase in the release of CTCs during the perioperative period. For example, patients with pancreatic cancer[13] might undergo a successful resection of a primary tumor, but still die from cancer recurrence due to new metastatic sites formed by the CTCs released during surgery.[14] Therefore, the perioperative period might be crucial for the individual patient's outcome and survival.

## ■ Anti-inflammatory Effects of Local Anesthetics Potentially Affecting Metastasis

### *Immune Modulation/Natural Killer (NK) Cell Activity*

During surgery, the patient's body faces a phenomenon called the "stress response": the release of several proinflammatory cytokines, such as interleukins and tumor necrosis factor α (TNFα), leads to a general proinflammatory state associated with the suppression of immune cell function.[15,16]

NK cells, a lymphocytic subset of the innate immune system,[17] are involved in the first line of defense against infected and malignant cells.[18,19] In rats, NK cell activity was significantly attenuated by stress

and by surgical procedures (laparotomy), which subsequently also led to an increase in the retention of inoculated tumor cells in these animals.[20] In humans undergoing surgery for breast, hepatocellular, or pulmonary carcinoma, a reduction of NK cell activity has also been observed.[21]

The influence of anesthetics on NK cell activity has been studied extensively. The volatile anesthetic halothane, for example, is known to decrease NK cytolytic activity in rats.[22] In addition, this finding was correlated with a subsequent increase in the retention of intravenously injected tumor cells in the lungs of the animals, whereas propofol did not have such an effect.[22] Experimental and clinical evidence also points toward a negative effect of opioids on NK cells, as it has been shown that morphine significantly depressed the cytolytic activity of these cells in rats and in healthy volunteers.[23,24] This effect could be demonstrated in cancer patients even after a single dose of morphine (10 mg intravenously) as early as 30 minutes after the administration of the drug.[25]

Local anesthetics might only have a detrimental effect on NK cell activity at very high (and certainly cytotoxic) concentrations in vitro.[26] In contrast, a very recent study showed that lidocaine at clinically relevant concentrations of 0.01 and 0.1 μM was able to enhance NK cytolytic activity in vitro through the release of lytic granules.[27] Similar results were obtained from a pilot study of patients undergoing breast cancer resection, who had either received a regional anesthetic (paravertebral block) in combination with propofol-based total intravenous anesthesia or intravenous opioids together with a sevoflurane general anesthetic; serum from women randomized to the regional/total intravenous anesthesia group induced a greater cytolytic activity in NK cells from healthy donors than serum from women who had been administered opioids and sevoflurane,[28] indicating a possible beneficial effect of regional anesthesia and local anesthetics with respect to NK cell activity in patients undergoing (breast) cancer surgery.

### *Endothelial Barrier, Leukocyte Activation, Leukocyte/ Tumor Cell Adhesion, and Transmigration*

The endothelial barrier plays an important role during the pathogenesis of metastasis, as the CTCs have to overcome this tight cell wall to invade the extracellular matrix at remote locations to form new metastatic sites.[29] Because of the surgical stress and the subsequent release of circulating, proinflammatory cytokines, such as TNFα, during surgery, endothelial barrier function might also be impaired.[30] TNFα activates nuclear factor κB (NFκB), a key mediator of inflammatory signaling in leukocytes, endothelial cells, and malignant cells,[31] as well as Src protein tyrosine kinase (Src).[31] Src activation, defined as Src autophosphorylation at tyrosine 419 and dephosphorylation of Src inhibitory phosphotyrosine 529,[32] is known to lead to a massive loss of

endothelial barrier function and a subsequent increase in vascular permeability,[32] which might enhance the extravasation of CTCs.[33] It has also been shown that this extravasation of malignant cells might depend on several events which are crucial for the recruitment and the adhesion of leukocytes to the endothelium and their subsequent transendothelial migration.[33] Intercellular adhesion molecule 1 (ICAM-1), for example, is not only expressed by endothelial cells,[34] but also by several different types of tumor cells[35–38] and is a key component for the adhesion of leukocytes to the endothelium.[39] Once phosphorylated at tyrosine 512 by Src, for example, upon stimulation with TNFα, ICAM-1 binds to CD11b (integrin αM) on the surface of polymorphonuclear cells (PMN) (neutrophil granulocytes, PMNs), which then leads to an enhanced adhesion and subsequent transmigration.[34,40] Binding of tumor cell ICAM-1 to PMN CD11b, might also occur and has been demonstrated to enhance the extravasation of CTCs significantly.[37,41]

The anti-inflammatory effects of local anesthetics are well known and have been studied extensively in vitro, in vivo, and in humans.[42,43] For instance, the amide-type local anesthetic ropivacaine was able to attenuate measures of acute lung injury such as pulmonary edema as well as neutrophil recruitment and transmigration after the instillation of bacterial lipopolysaccharide, as surrogates for the integrity of the endothelial barrier in vivo.[44,45] It was also shown that this in vivo protection might have been due to a decrease in Src and ICAM-1 expression/phosphorylation.[45] In vitro, it was demonstrated that ropivacaine was able to attenuate TNFα-induced signaling events in endothelial cells by blocking the initiating steps of signal propagation at the level of TNF receptor-1 right at the cell membrane, thus preserving endothelial barrier function and attenuating the adhesion of PMNs to the endothelium.[46] In addition, PMN activation and priming are also attenuated by local anesthetics.[47–50] Together with other evidence of certain protective, anti-inflammatory effects on the endothelium,[51,52] these results might indicate a potential beneficial effect of the use of local anesthetics in patients undergoing cancer surgery, as the extravasation of CTCs during the perioperative period might be impeded by the preservation of endothelial barrier function and by a decrease in the adhesion of leukocytes and cancer cells to the endothelium and their subsequent transendothelial migration.

### *Direct Effects on Cancer Cells: Inflammatory Signaling, Migration, Invasion, Epigenetics*

Besides the potentially beneficial effects of the perioperative use of regional anesthesia and local anesthetics in patients undergoing cancer surgery due to the preservation of endothelial barrier function[46] and a reduction in opioid consumption,[53] several recent studies were also able

to provide evidence for potential direct effects of local anesthetics on cancer cells, possibly due to their anti-inflammatory properties. In addition to its well-described role as a mediator of endothelial permeability, Src might also be involved in the migration, invasion, and extravasation of cancer cells.[54–56] On stimulation with TNFα, Src activation and ICAM-1 phosphorylation are increased significantly in lung adenocarcinoma cells in vitro, a phenomenon that was blocked by the amide-type local anesthetics lidocaine and ropivacaine, but not by the ester-type drug chloroprocaine.[6] This inhibition seemed to be independent of the blockade of the voltage-gated sodium channel and caused a significant decrease in the migratory abilities of the cells.[6] Further downstream of Src, the activation of Akt and focal adhesion kinase could be attenuated by clinically relevant concentrations of both lidocaine and ropivacaine, leading to a subsequent decrease in the production of matrix-metalloproteinase 9 (MMP-9) by the cancer cells.[57] MMPs are important enzymes for the breakup of the extracellular matrix during the invasion of cancer cells,[58–60] and therefore, the observed reduction in MMP secretion by the cancer cells after coincubation of the cells with TNFα and local anesthetics was also associated with a significant decrease in the invasiveness of the cells.[57] Although the described Src-dependent mechanisms might be independent of voltage-gated sodium channel blockade, another study also reported a decreased invasive potential of colon cancer cells in vitro due to the blocking of the sodium channel variant $Na_v1.5$ by ropivacaine.[61]

Apart from the outlined evidence for a potential beneficial effect of local anesthetics due to their anti-inflammatory properties, the drugs might also interfere with the regulation of gene expression, also known as epigenetics, by altering the methylation of DNA of malignant cells. Current evidence suggests that lidocaine is able to demethylate DNA of certain breast cancer cell lines at clinically relevant concentrations in vitro.[62] This effect was additive to that of a chemotherapeutic agent (5-aza-2′-deoxycytidine, DAC) and was also observed after incubation with ropivacaine, but not with bupivacaine.[63] Interestingly, this effect is the opposite compared with long-term opioid intake, which leads to hypermethylation.[64]

## ■ The Relevance of Perioperative Opioid Use in Cancer Surgery

Both the perioperative and the chronic use of opioids in the setting of malignancy has been traditionally considered to drive tumor progression and metastasis,[3] and a number of experimental studies have demonstrated enhanced growth of metastases in models such as intravenous tumor injection.[65] Among other effects, opioids have exper-

imentally been shown to act as immunosuppressants,[66] to increase angiogenesis,[67] and finally to promote metastasis.[68] In direct inoculation models, morphine administration favored tumor progression,[65] but other investigations were not able to replicate this effect.[69] However, many of these models did not mimic a slowly growing tumor, which metastasizes spontaneously, but rather used artificial inoculation.[70] In 1 recent model, which mirrored spontaneous breast cancer metastasis, the long-term administration of morphine did not lead to an increase in metastasis.[71,72] The same ambivalence can be found in the clinical literature regarding the clinical effects of morphine on tumor progression. Although some studies reported an association between morphine and a worsened tumor-related outcome (shortened recurrence-free interval, decreased patient survival),[73] other studies did not find similar effects. This might be explained by the heterogeneity of studies and tumor cell types, and the fact that the opiate requirement is, through tumor pain, linked to the tumor stage and progression,[74] and may reflect the patient's general condition more than playing a major clinical role per se.[75]

## ■ Clinical Evidence/Retrospective Analyses

During the last 15 years, several articles have been published dealing with the effects of regional anesthesia and cancer recurrence. All were retrospective, and large discrepancies in the results between the different studies were noted.

### *Positive Studies*

One of the first publications dealing with this topic came from the Tübingen group: Schlagenhauff and colleagues looked at the type of anesthesia performed for the excision of primary cutaneous melanoma. They retrospectively examined the follow-up data of 4329 patients. The authors found that there was a slight but significantly increased risk of death for patients treated with general anesthesia as compared with local anesthesia (no details concerning the procedures were noted).[76]

In 2006, Exadaktylos et al[77] hypothesized that breast cancer patients undergoing surgery with paravertebral anesthesia and analgesia combined with general anesthesia would have a better outcome than those having general anesthesia with postoperative intravenous morphine patient-controlled analgesia. Retrospectively, the authors found that recurrence and metastasis-free survival was 94% [95% confidence interval (CI), 87%-100%] and 82% (95% CI, 74%-91%) at 24 months and 94% (95% CI, 87%-100%) and 77% (95% CI, 68%-87%) at 36 months in the paravertebral and the general anesthesia groups, respectively ($P = 0.012$).[77] Patients in the paravertebral group received a 0.2 mL/kg

bolus of 0.25% levobupivacaine before the induction of general anesthesia, followed by a continuous infusion of 0.25% levobupivacaine for the first 48 hours postoperatively.

Two years later, another retrospective analysis investigated the influence of the use of epidural analgesia in patients undergoing radical prostatectomy for prostate cancer.[78] This work showed that the epidural group had a significantly lower risk of recurrence at 4, 6, 8, and 10 years after surgery as compared with the group that received general anesthesia only. In this investigation, the only provided information regarding the details of the epidural is the duration, which was reported between 48 and 72 hours postoperatively.

Long-term survival after the resection of colon cancer under general anesthesia with or without an epidural has subsequently been analyzed by Christopherson et al.[79] Analysis was performed regarding the presence or the absence of distant metastasis because this had the most significant effect on survival. The authors found that patients in the epidural group had an improved survival ($P = 0.012$) before a time frame of 1.46 years after surgery, whereas later, the type of anesthesia did not affect survival. Intermittent boluses of 0.5% bupivacaine were given. The duration of the epidural application was not specified.

Merquiol et al[80] retrospectively investigated the effect of cervical epidural anesthesia in patients undergoing surgery for laryngeal and hypopharyngeal cancer. Here, the primary outcome was the length of cancer-free survival. The results showed that the epidural group had a significantly better cancer-free survival of 68% at 5 years (95% CI, 57%-82%) against 37% (95% CI, 25%-34%) for the control group. Bupivacaine or ropivacaine were given for 48 hours postoperatively. The volume and the concentration of LA were not provided.

Another retrospective review of 143 patients undergoing surgery for ovarian serous adenocarcinoma with or without epidural reported 3- and 5-year overall survival rates of 78% and 60% in the epidural group against 58% and 49% in the control group.[81] After adjusting for the other variables, it was found that the control group had a hazard ratio of 1.214 ($P = 0.04$), suggesting a beneficial effect of the epidural in this setting. The epidural consisted of a continuous infusion of 0.125% bupivacaine or 0.15% ropivacaine for 48 hours postoperatively. The volume of LA administered was not specified in this study.

Positive effects of epidural anesthesia on the overall patient survival after cancer surgery have been shown in 2 meta-analyses, but tumor recurrence or metastatic disease was not affected.[82,83]

### Negative Studies

Myles and colleagues conducted a follow-up examination of patients previously enrolled in a randomized controlled clinical trial, the

multicenter Australian study of Epidural Anesthesia and Analgesia in Major Surgery, which had not been powered to investigate cancer recurrence.[84] The authors found that the median time to recurrence or death was 2.8 (95% CI, 0.7-8.7) against 2.6 years (95% CI, 0.7-8.7) in the epidural group ($P$ = NS). The major drawback of this work is that 50% of the epidurals apparently did not work, raising serious concerns about the validity of the results.

The effect of neuraxial anesthesia on the progression of cervical cancer was retrospectively examined in a small sample of 132 consecutive patients treated with brachytherapy.[85] The authors found that the use of neuraxial anesthesia during the first brachytherapy was not associated with a reduced risk of local or systemic recurrence (hazard ratio, 0.95%; 95% CI, 0.54-1.67; $P = 0.86$) or long-term mortality (hazard ratio, 1.46; 95% CI, 0.81-2.61; $P = 0.20$). No detailed information regarding the epidural procedure is available from this study.

Lacassie et al[86] conducted a retrospective analysis of patients undergoing laparotomy for ovarian cancer with or without epidural analgesia. After propensity score matching, the median time to recurrence was 1.6 and 1.4 years for the epidural and the control groups, respectively ($P = 0.3$). No details concerning the epidural procedure were given.

A large number of patients (> 27,000) were retrospectively analyzed regarding the effects of epidural analgesia against intravenous morphine on survival and cancer recurrence after colectomy.[87] The study revealed recurrence rates of 27.5% and 24.0% in the epidural and the control groups, respectively. In an adjusted logistic regression analysis, the incidence of recurrence was comparable in the 2 groups (odds ratio, 1.4; 95% CI, 0.96-2.05). No details concerning the epidural were given.

### Mixed Results

Gupta et al[88] retrospectively analyzed data of 655 patients who underwent laparotomy for gastrointestinal cancer with or without an epidural. Multivariate regression analyses showed that the epidural was associated with a reduction in all-cause mortality after rectal but not after colon cancer. The epidural consisted of either a local anesthetic alone or combined with fentanyl. No other details were provided.

Medical records of 182 patients undergoing surgery for ovarian cancer with (n = 55) or without (n = 127) epidural were analyzed retrospectively.[89] This investigation demonstrated that only patients with an epidural, which had been activated preoperatively, had a significantly better outcome, whereas patients with postoperative activation of the epidural had an outcome similar to that of the control

group with no epidural. No further information dealing with the epidural procedure was given.

In conclusion, there is a large discrepancy between the outlined investigations. One has to consider many drawbacks of these works including the tumor biology, the role of neoadjuvant and other chemotherapeutic treatments, and concomitant medications. Moreover, the documentation of the regional anesthetic technique—the key factor—should always include the concentration, the type, the dosage, and the duration of application of the local anesthetic. However, in the majority of the currently available investigations, this information has been insufficient and/or inadequate, especially in the negative studies. Without this basic information, no definitive conclusion can be made from these investigations and further well-designed prospective, randomized studies are needed.

Currently several randomized controlled trials are recruiting patients to verify (or disprove) the hypothesis that the perioperative use of local anesthetics could have an impact on survival or recurrence after cancer surgery. A recent Cochrane review lists only 4 different studies with a total of 746 patients,[90] including the already mentioned study by Myles et al.[84] The authors concluded that there is currently no definite evidence for a potential beneficial effect of the perioperative use of regional anesthesia in cancer patients.[90] However, as more results from randomized controlled trials are published, this might still change.

## ■ Scenarios of Local Anesthetic Application

In clinical practice, local anesthetics can be applied for infiltration anesthesia, regional anesthesia (spinal, epidural, and peripheral nerve blocks), and intravenously in the context of multimodal analgesia.[5]

During infiltration anesthesia, when a local anesthetic is applied around the tissue to be excised, millimolar concentrations of local anesthetics are attained at the site of injection adjacent to the tumor, and these concentrations have typically been associated with local anesthetic-induced cell death.[91] This might explain the protective effect of local anesthesia reported for melanoma excision under local anesthesia.[76] In contrast, systemic levels of local anesthetics reached after regional anesthesia or multimodal analgesia are typically in the low micromolar range.[92] In general, these settings represent the far ends of a spectrum on the one end of which lower micromolar concentrations are associated with the modulation of subcellular pathways, whereas on the other end at millimolar concentrations, direct cytotoxicity is observed.[46,62,93]

Whether perioperative regional anesthesia is indeed found to decrease tumor recurrence at least in some models,[4] the next major question to be addressed would be which exact component of regional anesthesia might

be responsible for this effect. Approximately 1 decade after the first major clinical trial demonstrating clinical benefits of intravenous lidocaine in visceral surgery patients,[43] we have come to realize that high-volume plexus blocks and epidural anesthesia are followed by the absorption of the local anesthetic into the systemic circulation, and that these local anesthetics are responsible for a substantial share of the beneficial effects of regional anesthesia, such as anti-inflammation and antihypercoagulability.[5] These latter effects might also be of relevance in tumor surgery. The intravenous application of lidocaine has been demonstrated firmly to have a beneficial effect after visceral surgery when considering acute outcome parameters such as the length of stay and the recovery of bowel function.[94] However, direct comparisons suggest that the efficacy of epidural anesthesia to attenuate the surgical stress response is superior to that of systemic local anesthetics alone.[95] The question of whether any potential antitumor effect of local anesthetics can be elicited by the intravenous administration of local anesthetics or whether it might be necessary to administer both (epidural or peripheral) nerve block and attain systemic levels in the bargain, remains to be defined.

## ■ Implications for Daily Practice and Outlook

The relevance of amide-type local anesthetics in the perioperative setting of tumor surgery is still debated, and there is currently no evidence to suggest that regional anesthesia techniques or intravenous local anesthetics should be considered as mandatory components for a comprehensive perioperative anesthesia plan for these patients.

However, there may be other good reasons to administer intravenous local anesthetics with or without regional anesthesia in patients undergoing cancer surgery. First, taking visceral surgery as a prototype, 2 recent meta-analyses demonstrated an improved overall survival when perioperative epidural anesthesia was used, although no difference in oncological parameters was observed.[82,83] Second, the incidence of chronic pain may be influenced by the type of analgesia. In particular, after thoracotomy and mastectomy, the incidence of chronic postsurgical pain is decreased when epidural or paravertebral blockade is performed.[96] A similar effect was noted after the combination of epidural and ketamine analgesia for laparotomy.[97] Therefore, the choice of regional technique, at the moment, should be based on the planned surgical procedure and on the individual patient, rather than on the specific malignancy.

## ■ Conclusions

The role of amide local anesthetics, whether administered for infiltration, regional anesthesia or intravenously, in the perioperative

care of tumor patients is still unclear. A substantial body of theoretical and experimental evidence suggests that by both direct and indirect effects, local anesthetics might be beneficial for the treatment of cancer patients. Clinical evidence still largely depends on underpowered and/or retrospective studies, and to date, the enthusiastic results from some animal trials have not been replicated in clinical practice. Adding to the complexity, the sheer biological diversity of human tumors, the array of local anesthetics available and their different routes of administration, as well as patient-specific considerations will most likely preclude a single and universal answer to the question of whether local anesthetics might have the potential to help reduce metastases. Currently, the choice to institute local, regional, or intravenous local anesthetics should be based on the surgical procedure and the patient status, and cannot be mandated on the basis of oncologic grounds.

The authors declare that they have nothing to disclose.

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